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Bridging the Gap Between Alleged Toxicity and Forcing Chemical Regulation: Science Transparency Demands a Specialized Interagency Peer Review Panel for Chemical Epidemiology

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Chemical epidemiology reports for all types of chemicals present in the environment are frequently published in the open literature. Such reports result in continuous controversy such as for glyphosate associated with non-Hodgkins lymphoma (Acquavella *et al.*, 2016; Pahwa *et al.*, 2019), paraquat associated with Parkinson's disease (Li *et al.*, 2005). Some of this controversy for chemical epidemiology studies may stem from a lack of transparency in data availability. For example, lack of transparency was evident when a recent attempt to obtain data to independently evaluate the neurodevelopmental effects in a chlorpyrifos epidemiology study (Rauh *et al.*, 2011) was unsuccessful (Dourson *et al.*, 2020).

Chemical epidemiology studies are based on the assumption that they may detect a subtle toxic response that occurs at much lower doses than conventional risk assessment models would predict and consequentially may have regulatory impact. When a chemical epidemiology study alleges an adverse outcome, it is a toxic response and thus the issue is very much a toxicologist's responsibility. These reports are often accepted at face value although they are conducted under a mixed bag of Good laboratory Practices, Quality Assurance, and ethics standards. There are many inherent problems especially associated with exposure and endpoint evaluation and very limited availability of the supporting data for independent analysis.

In contrast, animal studies submitted by industry are submitted in their entirety and are expected to follow current rigid Good Laboratory Practices, Quality assurance, and animal ethical standards. They are subjected to a costly multilevel agency review process. This disparity in the level of review for animal studies versus chemical epidemiology studies is neither serving the public well nor good science.

Mr Scott Pruitt, the former Administrator of the Environmental Protection Agency proposed a rule that studies used for risk assessment decisions must be transparent and supporting data must be available for independent review (Federal Register Notice. Strengthening Transparency in Regulatory Science. 40 CFR Part 30 Vol. 83, No. 83, Monday 30 April 2018.).

In order to promote transparency for chemical epidemiology studies it is proposed here that a *Specialized Interagency Peer Review Panel for Chemical Epidemiology Studies* be established. A suggested multidisciplinary composition is as follows: "Chairperson and Staff": Overall responsibility of the Panel including assigning projects to the Co-Chairs, conducting the Panel meetings, and coordinating the preparation of the Panel Report. "Co-Chairs (several)": Would be assigned the chemicals for review and coordinate the subcommittees. Having multiple Co-Chairs enables the Council to review multiple chemical issues concurrently.

Each issue would be independently evaluated by 6 subcommittees as follows: "Ethics": Many of the comments to Mr Pruitt's proposal were concerned that such a transparency rule would limit the willingness of people to participate because their privacy would be compromised. Further institutions conducting chemical epidemiology studies would also be unwilling to do so. However, transparency requires that the supporting data be made available for independent review. Therefore, the Ethics Subcommittee will have a critical role in developing

ethical standards for the study conduction and for data submissions. "Endpoint": Would consists of experts on the nature of the alleged adverse outcome including the etiology of the condition, factors known to affect it, subpopulation susceptibility and how large a cohort is needed to establish a true effect. Maintains a reference compendium of chemicals known or strongly suspected to cause adverse outcomes in humans as indicated by chemical epidemiology studies. "Statistics": Evaluates the statistical procedures as reported and determines the need for obtaining the original for independent analysis. "Exposure", "Analytical Chemistry", and "Animal Toxicity/ Structure Activity Relationships".

Current practices in some agencies have chemical epidemiology issues reviewed by their own Science Advisory Panels. However, these panels do not have uniform ethics standards, limit the expertise of the panel members, allow program politics and their decisions may vary from agency to agency. In order to assure independence and limit program politics the Co-Chair would not be from the agency responsible for the regulation of the chemical. Since there are many such chemical epidemiology reports occurring in the open literature, criteria for requesting a Panel review could be (but is not limited to) public interest groups suing the agency to stop the use of the chemical.

Upon completion of the subcommittees' reports, the Chairperson would convene a Panel meeting and subsequently prepare the Panel Report. In order to assure transparency, the Panel Report will clearly delineate its decisions with regard to the quality of the studies and assure that a significant adverse outcome is demonstrated or otherwise. If additional data are needed to assure transparency the Panel Report would advise how to procure it in a manner that preserves the privacy of the subjects. When appropriate, the Panel Report will advise on how to incorporate the adverse toxic outcomes into regulatory action. The completed Panel Report would then be made available to the public and if needed an additional meeting open to the public could be convened. Any affected party objecting to the decisions would need to clearly address the decisions of the Panel with supporting data or scientific rationale. Objectors cannot just say it is biased or make pandering passionate appeals.

There are advantages to the general public, activist interest groups, and industry since the Panel will: (1) Satisfy the need for transparency and assure that the decisions were based on sound science; (2) Provide a larger pool of qualified scientists; (3) Establish clear ethical standards that protect the privacy of individuals; (4) The independent nature of the Panel will reduce the political influence of the separate agencies responsible for regulation of the chemical; (5) Produce consistent conclusions for all agencies; and (6) Maintain a reference compendium of chemicals established to have adverse outcomes in chemical epidemiology studies.

In summary, this proposal is consistent with the mandate for transparency in risk assessment decisions as well as promoting rigor and objectivity in the evaluation of chemical epidemiology reports. The suggested rational for and composition as described above is presented to stimulate conversation on the need for and benefits of the proposed Panel. Any comments from concerned individuals are most welcome.

DECLARATION OF CONFLICTING INTERESTS

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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